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(54) Title: CONTROLLED RELEASE FORMULATION OF DIVALPROEX SODIUM

(57) Abstract

A controlled release tablet formulation which permits once daily dosing in the treatment of epilepsy comprises from about 50 weight percent to about 55 weight percent of an active ingredient selected from the group consisting of valproic acid, a pharmaceutically acceptable salt or ester of valproic acid, divalproex sodium, and valpromide; from about 20 weight percent to about 40 weight percent hydroxypropyl methylcellulose; from about 5 weight percent to about 15 weight percent lactose, from about 4 weight percent to about 6 weight percent microcrystalline cellulose, and from about 1 weight percent to about 5 weight percent silicon dioxide having an average particle size ranging between about 1 micron and about 10 microns; all weight percentages based upon the total weight of the tablet dosage form. Also disclosed are pre–tableting granular formulations, methods of making the granular formulations and tablets, and a method of treating epilepsy employing the controlled release tablet formulations of the invention.

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CONTROLLED RELEASE FORMULATION OF DIVALPROEX SODIUM

Technical Field

The present invention relates to pharmaceutical formulations. More particularly, the present invention concerns a formulation comprising valproic acid, a pharmaceutically acceptable salt, ester, or amide thereof or divalproex sodium, in a controlled release tablet formulation.

Background of the Invention

2-Propylpentanoic acid, more commonly known as valproic acid (VPA), its amide, valpromide (VPO), and certain salts and esters of the acid are effective in the treatment of epileptic seizures or as antipsychotic agents. United States Patent 4,988,731 to Meade discloses an oligomer having a 1:1 molar ratio of sodium valproate and valproic acid containing 4 units, and United States Patent 5,212,326 to Meade discloses a stable, non-hygroscopic solid form of valproic acid which comprises an oligomer having 1:1 molar ratio of sodium valproate and valproic acid and containing four to six units. Divalproex sodium (sodium hydrogen divalproate) is one of the most widely accepted antiepileptic agents currently available.

However, despite its efficacy in the treatment of epilepsy, valproic acid has been shown to exhibit an elimination half-life which is shorter than other commonly used anti-epileptic agents. Half-lives for the drug of between six and seventeen hours in adults and between four and fourteen hours in children have been reported. This leads to substantial fluctuations in the plasma concentration of the drug, especially in chronic administration. To maintain reasonably stable plasma concentrations, it is necessary to resort to frequent dosing, and the resulting inconvenience to the patient often results in lowered compliance with the prescribed dosing regimen. Moreover, widely fluctuating plasma concentrations of the drug may result in administration of less than therapeutic amounts of the drug in a conservative dosing regimen, or amounts too large for the particular patient in an aggressive dosing regimen.

To overcome this disadvantage, a concerted effort has been devoted to the discovery of valproic acid formulations which will maintain more constant plasma levels of the drug following administration. The ultimate goal of these studies has been the discovery of a formulation which affords stable plasma levels in a once-a-day dosing regimen. These efforts fall generally into one of two categories: (a) finding a form of the active ingredient which is more slowly released to the body metabolically, and (b) finding a formulation which delivers the drug by either a timed- or controlled-release mechanism.

United States Patent 4,369,172 to Schor, *et al.* describes, for example, a prolonged release therapeutic composition based on mixtures of hydroxypropyl methylcellulose, ethyl cellulose and/or sodium carboxymethyl cellulose. The patentees provide a long list of therapeutic agents which they suggest can be incorporated into the formulation including sodium valproate.

United States Patent 4,913,906 to Friedman, *et al.* discloses a controlled release dosage form of valproic acid, its amide, or one of its salts or esters in combination with a natural or synthetic polymer, pressed into a tablet under high pressure.

United States Patent 5,009,897 to Brinker, *et al.* discloses granules, suitable for pressing into tablets, the granules comprising a core of divalproex sodium and a coating of a mixture of a polymer and microcrystalline cellulose.

United States Patent 5,019,398 to Daste discloses a sustained-release tablet of divalproex sodium in a matrix of hydroxypropyl methylcellulose and hydrated silica.

United States Patent 5,055,306 to Barry, *et al.* discloses an effervescent or water-dispersible granular sustained release formulation suitable for use with a variety of therapeutic agents. The granules comprise a core comprising the active ingredient and at least one excipient, and a water insoluble, water-swellable coating comprising a copolymer of ethyl acrylate and methyl methacrylate and a water soluble hydroxylated cellulose derivative. The patentees suggest a list of therapeutic agents which may be used in the formulation of the invention, including sodium valproate.

United States Patent 5,169,642 to Brinkler, *et al.* discloses a sustained release dosage form comprising granules of divalproex sodium or amides or esters of valproic acid coated with a sustained release composition comprising ethyl cellulose or a methacrylic methyl ester, a plasticizer, a detackifying agent, and a slow-release polymeric viscosity agent.

United States Patent 5,185,159 to Aubert, *et al.* discloses a formulation of valproic acid and sodium valproate which is prepared without the use of either a binder or a granulating solvent. The formulation optionally contains precipitated silica as an anti-sticking or detackifying agent.

United States Patent 5,589,191 to Exigua, *et al.* discloses a slow release sodium valproate tablet formulation in which the tablets are coated with ethyl cellulose containing silicic acid anhydride.

Published PCT application WO 94/27587 to Ayer, *et al.* discloses a method for control of epilepsy by delivering a therapeutic composition of valproic acid or a derivative in combination with a poly(alkylene oxide).

Bialer, *et al.*, "Metabolism of Antiepileptic Drugs," pp. 143-151, R. H. Levy, Ed., Raven Press, New York, 1984; Int. J. Pharmaceutics, **20**: 53-63 (1984); and Biopharmaceutics and Drug Disposition, **6**: 401-411 (1985); and Israel J. Med. Sci., **20**: 46-49 (1995) report the pharmacokinetic evaluation of several sustained release formulations of valproic acid.

There remains, however, the need for a sustained release formulation of valproic acid which will effectively maintain plasma concentrations of the drug at more constant levels.

Summary of the Invention

The present invention provides, in its principal embodiment, a controlled release tablet dosage form comprising from about 50 weight percent to about 55 weight percent of an active ingredient selected from the group consisting of valproic acid, a pharmaceutically acceptable salt or ester of valproic acid, divalproex sodium, and valpromide; from about 20 weight percent to about 40 weight percent hydroxypropyl methylcellulose; from about 5 weight percent to about 15 weight percent lactose, from about 4 weight percent to about 6 weight percent microcrystalline cellulose, and from about 1 weight percent to about 5 weight percent silicon dioxide having an average particle size ranging between about 1 micron and about 10 microns; all weight percentages based upon the total weight of the tablet dosage form.

The tablet provides the active pharmaceutical in a hydrophilic matrix which slowly releases the active agent over a prolonged period of time in such a manner as to provide substantially level plasma concentrations of the drug following once-a-day dosing.

In an alternative embodiment, the present invention provides a dry granular composition suitable for compressing into a tablet dosage form, the granular composition comprising particles of a size smaller than about 1 mm comprising from about 50 weight percent to about 55 weight percent of an active ingredient selected from the group consisting of valproic acid, a pharmaceutically acceptable salt or ester of valproic acid, divalproex sodium, and valpromide; from about 20 weight percent to about 40 weight percent hydroxypropyl methylcellulose; from about 5 weight percent to about 15 weight percent lactose, from about 4 weight percent to about 6 weight percent microcrystalline cellulose, and from about 1 weight percent to about 5 weight percent silicon dioxide having an average particle size ranging between about 1 micron and about 10 microns; all weight percentages based upon the total weight of the granular composition.

In a further embodiment, the present invention provides a granular composition suitable for pressing into a controlled release tablet dosage form comprising the steps of a) dry blending a mixture of from about 50 weight percent to about 55 weight percent divalproex sodium, from about 20 weight percent to about 40 weight percent hydroxypropyl methylcellulose, and from about 5 weight percent to about 15 weight percent lactose to form a uniform mixture of the dry ingredients; b) wet granulating the dry uniform mixture from step a); c) drying and sizing the wet granules from step b) to select granules having an average size below 1 mm; and d) dry blending the granules with from about 4 weight percent to about 6 weight percent microcrystalline cellulose, and from about 1 weight percent to about 5 weight percent silicon dioxide having an average particle size ranging between about 1 micron and about 10 microns, or the microcrystalline cellose can be dry blended in step (a) with the divalproex sodium, hydroxypropyl methylcellulose and lactose.

In yet another embodiment, the present invention provides a method of preparing a controlled release tablet dosage form of divalproex sodium comprising the steps of a) dry blending a mixture of from about 50 weight percent to about 55 weight percent divalproex sodium, from about 20 weight percent to about 35 weight percent hydroxypropylmethyl

cellulose, from about 5 weight percent to about 15 weight percent lactose to form a uniform mixture of the dry ingredients; b) wet granulating the dry uniform mixture from step a); c) drying and sizing the wet granules from step b) to select granules having an average size below 1 mm; d) dry blending the granules with from about 4 weight percent to about 6 weight percent microcrystalline cellulose, and from about 1 weight percent to about 5 weight percent silicon dioxide having an average particle size ranging between about 1 micron and about 10 microns; and e) compressing the blended granules of step h) under a force ranging between about 2000 lbf (about 8.9×10^3 Newtons) and 10,000 lbf (about 4.45×10^4 Newtons). In a similar manner, the microcrystalline cellulose can be dry blended in step (a) with the divalproex sodium, hydroxypropyl methylcellulose and lactose.

Brief Description of the Drawings

In the drawings, which form a part of this specification:

FIGURE 1 is a graphical representation of the release of drug from several test controlled release tablet formulations under *in vitro* conditions.

FIGURE 2 is a graphical representation of *in vitro* release of drug from two preferred controlled release tablet formulations of the invention.

FIGURE 3 is a graphical representation of plasma concentration in human subjects following administration of two of the preferred controlled release tablet formulations of the invention.

FIGURE 4 is a graph showing plasma concentrations of valproic acid in a human subject following multiple administrations of a preferred controlled release formulation of the invention.

Detailed Description

As used throughout this specification and the appended claims, the terms "sustained release," "prolonged release," and "controlled release" as applied to drug formulations have the meanings ascribed to them in "Remington's Pharmaceutical Sciences," 18th Ed., p.1677, Mack Pub. Co., Easton, PA (1990). Sustained release drug systems include any drug delivery system which achieves the slow release of drug over an extended period of time, and include both prolonged and controlled release systems. If such a sustained release system is effective in maintaining substantially constant drug levels in the blood or target tissue, it is

considered a controlled release drug delivery system. If, however, a drug delivery system is unsuccessful at achieving substantially constant blood or tissue drug levels, but nevertheless extends the duration of action of a drug over that achieved by conventional delivery, it is considered a prolonged release system.

The formulations of the present invention provide a controlled release formulation for valproic acid. The term "valproic acid" is meant to encompass the compound 2-propylpentanoic acid *per se*, and its pharmaceutically acceptable salts, and compounds which readily metabolize *in vivo* to produce valproic acid, such as valproic acid amide (valpromide), as well as other pharmaceutically acceptable amides and esters of the acid. A particularly preferred form of valproic acid for the compositions of the present invention is the complex formed between one mole of 2-propylpentanoic acid and its sodium salt, commonly referred to a "divalproex sodium." Divalproex sodium is disclosed in United States Patents 4,988,731 and 5,212,326 to Meade and can be represented by the following formula where m ranges from two to about six:

Experimental

One gram tablets containing 538 mg of divalproex sodium, magnesium stearate, dicalcium phosphate, microcrystalline cellulose (Avicel®, FMC Corporation, Philadelphia, PA, USA) and/or lactose and various hydrophilic polymers were prepared. Hydrophilic polymers tested included hydroxypropyl methylcellulose, methylcellulose (Methocel® grades K100LVP CR, K4MP CR, K15MP CR and K100MP CR, Dow Chemical, Midland, MI,

USA); hydroxypropyl cellulose (Klucel® LF, Hercules, Inc., Wilmington, DE, USA); and alginate (Keltone® grades LVCR and HVCR, Kelco Co., San Diego, CA, USA).

Bulk drug was milled prior to use and was sized to pass a 40 mesh sieve (0.42 mm nominal mesh opening). The milled and sieved bulk drug was dry-mixed with polymer and excipients in a Collette Gral 10 high shear mixer for 5 min at a high chopper speed of 3000 rpm and impeller speed of 200 rpm. Granules were prepared by adding 70 ml/kg of granulation fluid (water or water/ethanol mixtures) to the polymer/drug/excipient powder mixture over a 1-2 minute period at high chopper speed of 3000 rpm and impeller speed of 500 rpm. Additional fluid of 10-165 ml was added in one step as needed in order to reach granulation end-point. Total granulation time ranged from 2-18 min.

Tablet matrix ingredients included microcrystalline cellulose, lactose, magnesium stearate, and silicon dioxide. The resulting granules were tray dried at 50°C-55°C overnight under reduced pressure. The dried granules were mixed with lubricant (magnesium stearate) in a bag and then passed through a 20 mesh (0.84 mm nominal opening) sieve. Tablets weighing 1 g were pressed in a Model C Carver Press tableting machine using a 0.747 inch (1.9 cm) x 0.360 inch (0.91 cm) ovaloid die at a compression force between about 2000 lbf (about 8.9×10^3 Newtons) and about 10,000 lbf (about 4.45×10^4 Newtons), preferably between about 2300 lbf (1.02×10^4 Newtons) to about 5000 lbf (2.25×10^4 Newtons). The tablet compositions are presented in Table 1.

Table 1

Test Divalproex Matrix Tablet Formulations

Ingredient[1]	A	B	C	D	E	F	G	H	I
Divalproex sodium	50	50	50	50	50	53.8	53.8	53.8	53.8
Methocel® K100LVPCR	18	20	-	-	-	-	-	-	10
Methocel® K4MPCR	8	-	-	-	-	-	-	-	-
Klucel® LF	-	20	-	-	-	-	-	-	-
Keltone® HVCR	-	-	30	-	-	-	-	-	-
Methocel® K15MPCR	-	-	-	-	30	26	35	-	16
Methocel® K100MPCR	-	-	-	15	-	-	-	30	-
Lactose	23	9.5	9.5	29.5	14.5	14.7	5.7	10.7	14.7
Avicel® PH101	-	0	5	5	5	5	5	5	5
PVP[2]	-	-	5	-	-	-	-	-	-
Magnesium Stearate	1	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

[1] Percent by weight, based upon the total tablet weight
[1] Poly(vinylpyrrolidone)

Initial Formulation Screening

Initial screening of the matrix tablet formulations was performed using a number of tests. Tablet hardness for each formulation was measured using a Model VK2000 VanKel tablet hardness analyzer and recorded in units of kiloPascals (kP) as the average of ten trials.

Friability of the tablets were tested by rotating the tablets samples 100 times using a Erweka TA friabilator. Friability of tablets for each formulation were calculated based on the weight loss of the tablets in this test.

Bulk density of the formulation granules was measured by carefully filling a glass graduated cylinder to the 100 ml mark. Tap density was determined following 100 taps of the filled cylinder.

Determination of granule size distribution was performed by collecting granules larger than 140 mesh (about 0.105 mm nominal mesh opening) and 40 mesh (about 0.42 mm nominal mesh opening) for evaluation of the percentage of fines and large granules.

In vitro dissolution tests were conducted using Apparatus II described in the *United State Pharmacopeia* XXI/*National* Formulary XVI. Samples aliquots of 1.5 ml were withdrawn and filtered through a 0.45 μm filter and assayed by TDX® fluorescent polarization immunoassay. Upon withdrawal of each sample, an equal volume of medium was added to the test mixture to maintain constant volume. The test conditions were as follows:

Apparatus	USP II, paddle
Medium	1M HCl for one hour; remaining time pH 6.8 buffer
Volume of medium	900 ml
Temperature	37°C ± 0.5°C
Paddle speed	100 rpm
Sampling volume	1.5 ml
Sampling times	0, 0.5, 1, 2, 4 ,6, 8, 13, 24 hours

The results of these tests are presented in Table 2.

Based upon these initial studies, and the data appearing in Table 2 above, the following conclusions were drawn:

(1) Effects on tablet hardness: The use of ethanol as a granulation fluid tends to increase tablet hardness. There is a strong interaction between ethanol and particle size of

the bulk drug. The increase in hardness was only observed for formulations containing drug of larger particle size. The opposite effect was found for drug of smaller particle size.

(2) Effects on friability: The use of drug having a small particle size reduced friability. However, this effect was significant only for formulations using water as granulation fluid.

(3) Effects on density: The use of ethanol as a granulation fluid was shown to decrease the density of the granules. However, significant interactions of ethanol with the use of Klucel®, and of ethanol with drug particle size were observed. Ethanol decreased the density only of formulations containing drug of larger particle size and/or formulations without Klucel® present. The opposite effects were found for formulations containing smaller drug particles and/or Klucel®. The same conclusions were obtained with either tap or bulk density as response.

(4) Effects on size of granules: More granules of larger size were obtained with the use of drug having a larger particle size. Moreover, interaction between ethanol and Klucel® was found to be significant i.e. use of ethanol tends to generate larger granules when there is no Klucel® present in the formulation. No effect was observed for formulations containing 4% Klucel®. Factors that showed significant influences on the percentage of fines in the granules included ethanol, drug particle size, and their interaction. Using smaller drug particles tended to yield more fines in the granules. More fines were generated when ethanol was used as a granulation fluid. The effect of ethanol was most significant for formulations containing drug of a small particle size.

(5) Effects on granulation fluid volume: In order to obtain granulation end-point, more fluid volume was needed for formulations containing either drug of a smaller particle size or with the use of ethanol as granulation fluid.

(6) In vitro drug release: *In vitro* percent release of valproic acid from controlled-release tablets are shown in Figure 1. The difference in release profiles among formulations was small. In the study, percent release at 8 hours (Q_{8hr}) was used to represent release rate for data analysis. It was found that the use of Klucel® or drug of a larger particle size in the formulation resulted in an increase in release rate. Similar results were obtained when Q_{10hr} or Q_{24hr} was used to estimate the release rate.

Formulations containing high load and high viscosity grades of polymers often showed poor compressibility. This is believed to be the result of the increase in polymer order and elasticity with increasing molecular weight. Hardness of the tablets remained almost unchanged under compression forces ranging from about 3000 lb (1.3×10^4 Newtons) to about 10,000 lb (4.45×10^4 Newtons).

Table 2

Form-ulation	Granulating Fluid Volume	Hardness (kP)	Friability (% Loss)	Tap Density (g/ml)	Bulk Density (g/ml)	% Granule Size >40 Mesh	Fines [1]	$Q_{8\,hr}$ (%)[2]
A	100	11.9	0.049	0.504	0.429	22.6	6.1	27.6
B	80	7.2	0.16	0.515	0.438	31.3	9.8	29.0
C	115	12.2	0.025	0.459	0.39	30.2	3.3	28.6
D	80	8.4	0.162	0.459	0.406	38.2	6.6	30.4
E	235	10.4	0.060	0.599	0.509	21.5	40.7	27.0
F	110	12.2	0.006	0.400	0.340	49.2	1.8	28.0
G	200	9.4	0.085	0.596	0.506	24.0	29.7	29.7
H	150	12.9	0.142	0.593	0.504	35.0	22.8	30.0
I	130	9.5	0.015	0.475	0.404	33.8	1.2	28.8

[1] Defined as percent granules passing a 0.105 mm nominal mesh opening

[2] Defined as percent drug released in an 8-hour period under the *in vitro* test conditions

In order to increase the hardness of tablets, microcrystalline cellulose and colloidal silicon dioxide were tested by externally adding small amounts to the granules at levels of 1-5%. Table 3 shows the results from the test. It was found that external addition of small amounts of microcrystalline cellulose or colloidal silicon dioxide significantly increased tablet hardness.

Table 3

Effect of External Addition of Microcrystalline Cellulose or Silicon Dioxide

Hardness Test Formulation	Additive	Hardness (kP)
Ia	None	6.2
Ib	5% Avicel®	9.6
Ic	5% Avicel® and 1% silicon dioxide[1]	13.8
IIa	None	---
IIb	1% Silicon dioxide[1]	10.9
IIc	5% Avicel® and 1% silicon dioxide[1]	14.4
IIIa	None	5.8
IIIb	1% Silicon dioxide[1]	10.8
IIIc	5% Avicel® and 1% silicon dioxide[1]	14.8

[1] Silicon dioxide was Cab-O-Sil M-5 fumed silica (Cabot Corp., Boyertown, PA, USA) having average particle size of between about 0.2 and 0.3 microns

As shown by the data in Table 3, the addition of either 1% silicon dioxide or 5% microcrystalline cellulose to the hydrophilic matrix formulations of the invention almost doubled tablet hardness, while adding both resulted in a greater than doubling of tablet

hardness. However, although the results shown above demonstrated improvement of tablet hardness by the combined use of the external addition of Avicel® microcrystalline cellulose and Cab-o-sil® silicon dioxide, problems of sticking and relatively low density persisted. The low bulk density (i.e. 40 g/l) of the small particle size Cab-O-Sil® fumed silica led to the problem of not being able to load sufficient material into the tablet die.

In response to this problem, a different silicon dioxide having a larger average particle size ranging from about 1 micron to about 10 microns, preferably ranging between about 2 microns to about 5 microns, and most preferably about 2-3 microns was used. One such material is available as Syloid® 244, available from W. R. Grace, Lexington, MA, USA. When this material was used, initially intended as a de-tackifying and hardening agent for tableting, a surprising and unexpected benefit was conferred upon the formulation, as shown below. The material was added "externally" to the formulation: that is, the active ingredient, polymer(s) and excipients were dry blended, wet granulated, and then dried and sized. The silicon dioxide was then added to the granular formulation and the resulting mixture blended prior to pressing into tablets.

On the basis of the above findings, preferred tablet formulations were chosen for an *in vivo* absorption study in healthy human subjects. The ingredients of the formulations and *in vitro* release rates are shown in Table 4 and Figure 2, respectively. The formulations were designed to have different release rates by using high viscosity HPMC alone or blended with low viscosity HPMC. The target *in vitro* release rates were chosen to release drug *in* vivo for 16-20 hours.

Using the two preferred formulations described in Table 4, two *in vivo* studies in human subjects were carried out. Figure 3 shows the mean plasma concentration-time profiles of valproic acid in humans following a single oral dose of the two formulations. It was found that preferred formulations A and B provided prolonged absorption of valproic acid for approximately 10 hours and 24 hours respectively. It was apparent that the slower releasing formulation, tablet B, showed more desirable sustained plasma levels. Therefore, this formulation was further tested in a multiple dose study in healthy human subjects at an oral dose of 1 gram given once daily. The results shown in Figure 4 indicated that mean

steady-state plasma levels were well controlled between 62.3 and 78.2 μg/ml with minimal fluctuation, which falls within the therapeutic range of valproic acid (30-100ug/ml).

Table 4

Preferred Controlled Release Formulations of the Invention

Ingredient	Preferred Formulation A	Preferred Formulation B
Divalproex sodium (milled)[1]	53.82%[2]	53.82%
Hydroxypropyl methylcellulose (Methocel® K15M, CR)	8%	30%
Methyl cellulose (Methocel® K100L, CR)	18%	---
Anhydrous lactose	12.18%	8.18%
Microcrystalline cellulose (Avicel® PH 101)	5%	5%
Silicon dioxide (Average particle size 1 μm< >10 μm) (Syloid® 244)	3%	3%
Total tablet weight	1 g	1g

[1] Bulk drug sized to pass a 40 mesh sieve (0.42 mm nominal mesh opening

[2] All percentages in the Table expressed as weight percentages based upon the total weight of the tablet

The controlled release tablet formulations of the present invention thus provide an effective delivery system for the once daily administration of valproic acid (divalproex sodium) to patients in need of such treatment. The formulations of the invention provide substantially level plasma concentrations of valproic acid falling within the therapeutic range of the drug over a period which permits administration once daily.

While there have been shown and described what are the preferred embodiments of the invention, one skilled in the pharmaceutical formulation art will appreciate that various modifications in the formulations and process can be made without departing from the scope of the invention as it is defined by the appended claims.

WE CLAIM:

1. A controlled release tablet dosage form comprising

a) from about 50 weight percent to about 55 weight percent of an active ingredient selected from the group consisting of valproic acid, a pharmaceutically acceptable salt or ester of valproic acid, divalproex sodium, and valpromide,;

b) from about 20 weight percent to about 40 weight percent hydroxypropyl methylcellulose;

c) from about 5 weight percent to about 15 weight percent lactose, from about 4 weight percent to about 6 weight percent microcrystalline cellulose, and from about 1 to about 5 weight percent silicon dioxide having an average particle size ranging between about 1 micron and about 10 microns;

all weight percentages based upon the total weight of the tablet dosage form.

2. A controlled release tablet dosage form according to Claim 1 wherein said active ingredient is divalproex sodium.

3. A controlled release tablet dosage form according to Claim 1 wherein said hydroxypropyl methylcellulose is present in an amount of between about 20 weight percent and about 40 weight percent, based on the total weight of the tablet dosage form.

4. A controlled release tablet dosage form according to Claim 1 wherein said silicon dioxide has an average particle size ranging between about 2 microns and about 5 microns.

5. A controlled release tablet formulation comprising about 54 weight percent divalproex sodium, about 30 weight percent hydroxypropyl methylcellulose, about 8 weight percent lactose, about 5 weight percent microcrystalline cellulose, and about 3 weight percent silicon dioxide having an average particle size ranging from about microns to about 2 microns to about 5 microns.

6. A granular composition for pressing into a controlled release tablet dosage form, having a particle size ranging between about 0.100 mm and about 0.84 mm comprising

a) from about 50 weight percent to about 55 weight percent of an active ingredient selected from the group consisting of valproic acid, a pharmaceutically acceptable salt or ester of valproic acid, divalproex sodium, and valpromide;

b) from about 20 weight percent to about 35 weight percent hydroxypropyl methylcellulose;

c) from about 5 weight percent to about 15 weight percent lactose,

d) from about 4 weight percent to about 6 weight percent microcrystalline cellulose, and

e) from about 1 to about 5 weight percent silicon dioxide having an average particle size ranging between about 1 micron and about 10 microns;

all weight percentages based upon the total weight of the granular composition.

7. The granular composition of Claim 6 wherein said active ingredient is divalproex sodium.

8. The granular composition according to Claim 7 wherein said hydroxypropyl methyl cellulose is present in an amount of between about 25 weight percent and about 40 weight percent, based on the total weight of the tablet dosage form.

9. The granular composition according to Claim 7 wherein said silicon dioxide has an average particle size ranging between about 2 microns and about 5 microns.

10. A granular composition for pressing into a controlled release tablet dosage form comprising about 54 weight percent divalproex sodium, about 30 weight percent hydroxypropyl methylcellulose, about 8 weight percent lactose, about 5 weight percent microcrystalline cellulose, and about 3 weight percent silicon dioxide having an average particle size ranging from about microns to about 2 microns to about 5 microns.

11. A method of preparing a granular composition suitable for pressing into a controlled release tablet dosage form comprising the steps of:

a) dry blending a mixture of from about 50 weight percent to about 55 weight percent divalproex sodium, from about 20 weight percent to about 40 weight percent hydroxypropyl methylcellulose, and from about 5 weight percent to about 15 weight percent lactose to form a uniform mixture of the dry ingredients;

b) wet granulating the dry uniform mixture from step a);

c) drying and sizing the wet granules from step b) to select granules having an average size below about 0.84 mm; and

d) dry blending the granules with from about 4 weight percent to about 6 weight percent microcrystalline cellulose, and from about 1 to about 5 weight percent silicon dioxide having an average particle size ranging between about 1

micron and about 10 microns.

12. A method of preparing a controlled release tablet dosage form of divalproex sodium comprising the steps of:

a) milling bulk divalproex sodium and sizing it to have an average particle size less than about 0.5 mm;

b) dry blending a mixture of from about 50 weight percent to about 55 weight percent divalproex sodium, from about 20 weight percent to about 35 weight percent hydroxypropyl methylcellulose, and from about 5 weight percent to about 15 weight percent lactose to form a uniform mixture of the dry ingredients;

c) wet granulating the dry uniform mixture from step a);

d) drying and sizing the wet granules from step b) to select granules having an average size below 1 mm; and

e) dry blending the granules with from about 4 weight percent to about 6 weight percent microcrystalline cellulose, and from about 1 to about 5 weight percent silicon dioxide having an average particle size ranging between about 1 micron and about 10 microns; and

f) compressing the blended granules of step h) under a force ranging between about 2000 lbf (about 8.9×10^3 Newtons) and 10,000 lbf (about 4.45×10^4 Newtons).

13. The method of Claim 12 wherein said silicon dioxide has an average particle size ranging between about 2 microns and about 5 microns.

14. +-69A method of treating epilepsy comprising administering once daily to a patient in need of such treatment a controlled release tablet dosage form comprising a daily therapeutic dose of divalproex sodium in a matrix comprising:

a) from about 20 weight percent to about 40 weight percent hydroxypropyl methylcellulose;

b) from about 5 weight percent to about 15 weight percent lactose;

c) from about 4 weight percent to about 6 weight percent microcrystalline cellulose: and

d) from about 1 to about 5 weight percent silicon dioxide having an average particle size ranging between about 1 micron and about 10 microns;

all weight percentages based upon the total weight of the tablet dosage form.

15. The method of Claim 14 wherein said silicon dioxide has an average particle size ranging between about 2 microns and about 5 microns.

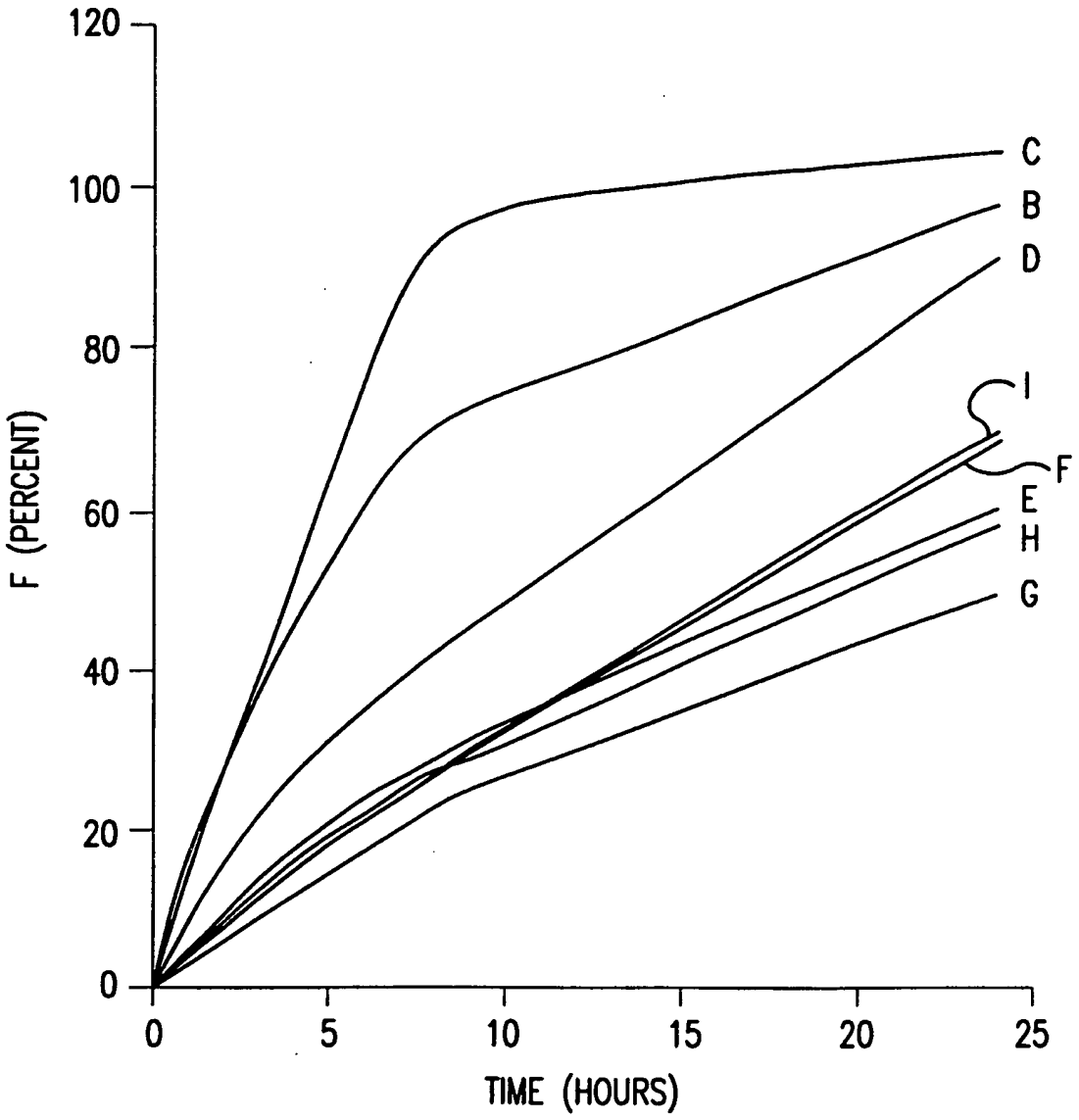

120
100
80
60
40
20
0
F (PERCENT)
0
5
10
15
20
25
TIME (HOURS)
C
B
D
I
F
E
H
G

FIG.1

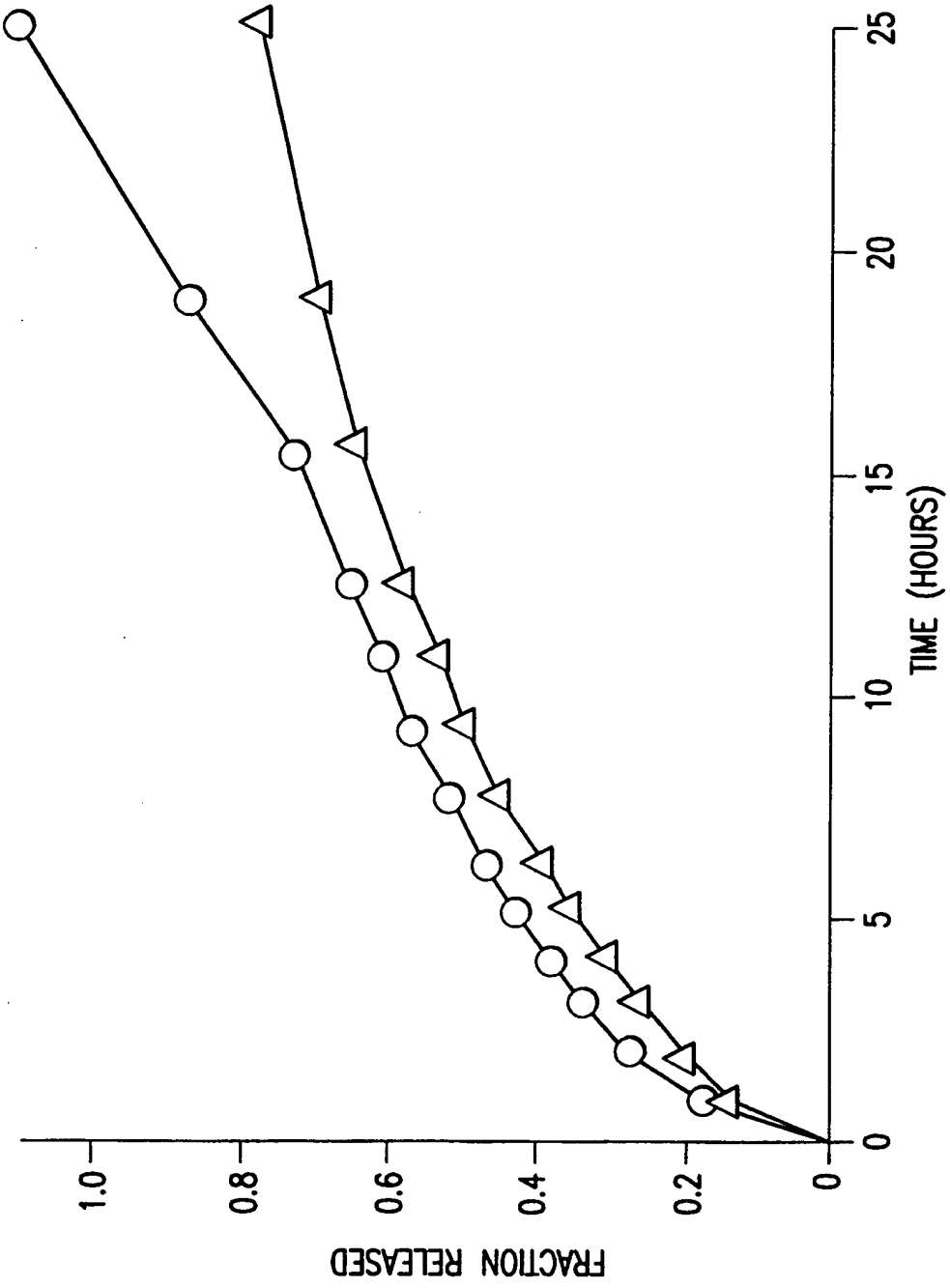
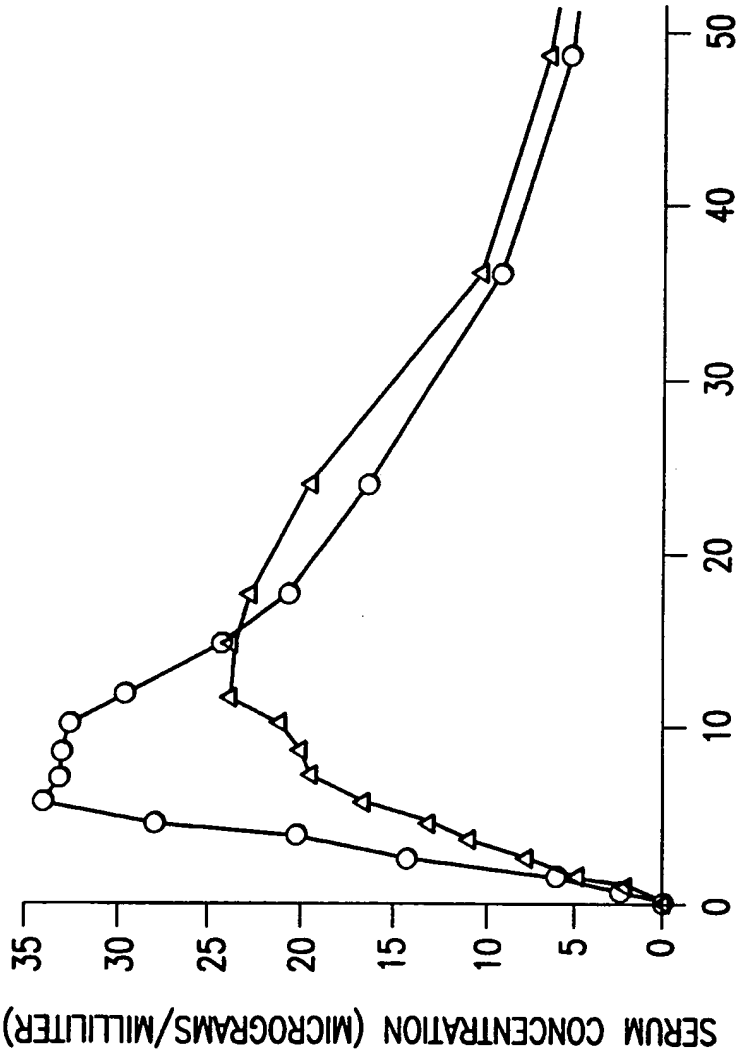


FIG.2


SERUM CONCENTRATION (MICROGRAMS/MILLILITER)
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30
25
20
15
10
5
0
0
10
20
30
40
50
TIME AFTER ADMINISTRATION

FIG.3

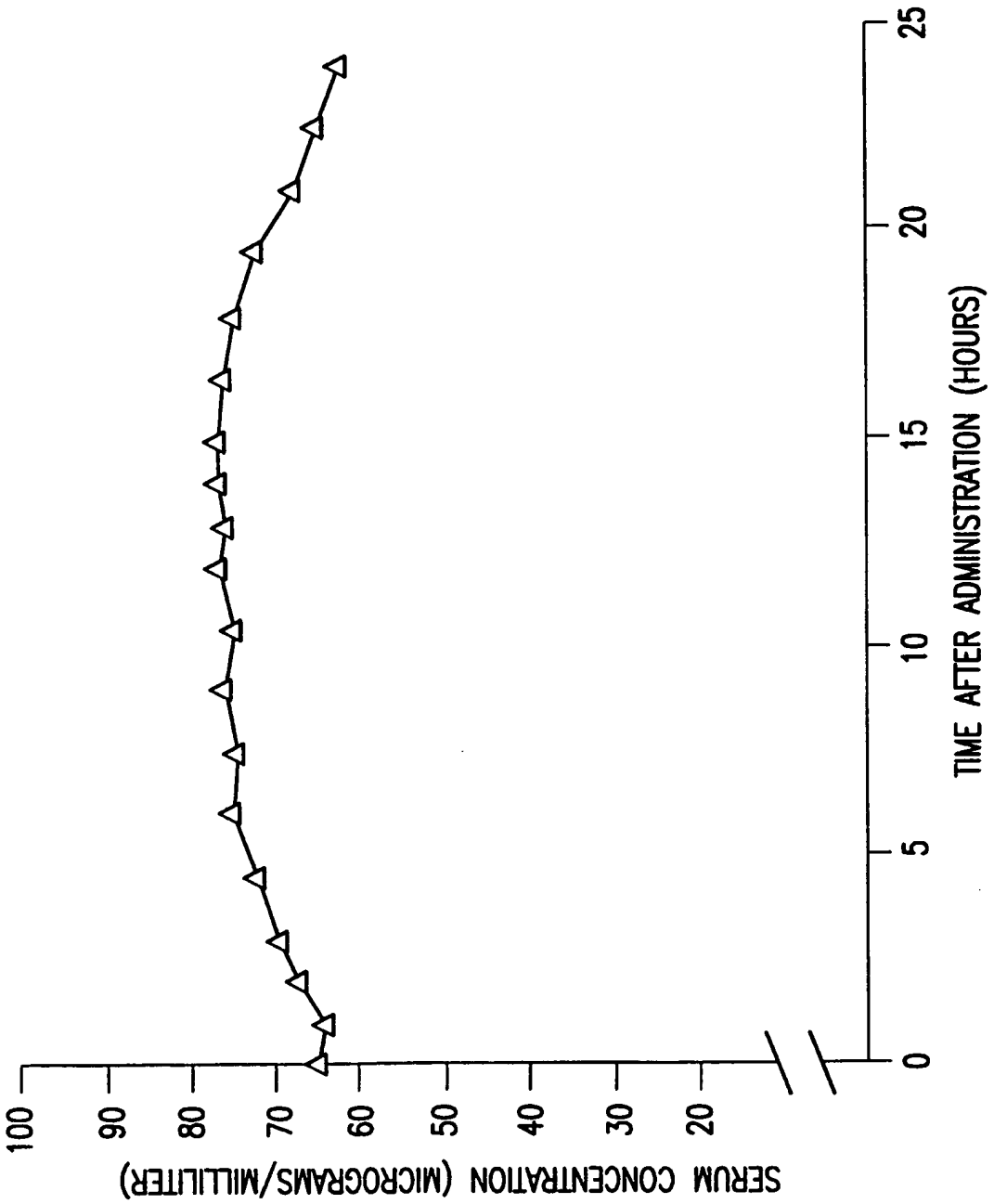
SERUM CONCENTRATION (MICROGRAMS/MILLILITER)
100
90
80
70
60
50
40
30
20
0
5
10
15
20
25
TIME AFTER ADMINISTRATION (HOURS)

FIG.4

INTERNATIONAL SEARCH REPORT

Im dional Application No
PCT/US 99/29204

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/22 A61K9/16 A61K31/19 A61K31/16 A61P25/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 019 398 A (DASTE GEORGES) 28 May 1991 (1991-05-28) cited in the application column 1, line 43 -column 2, line 3 example claims ---	1-15
A	US 5 009 897 A (BRINKER DALE R ET AL) 23 April 1991 (1991-04-23) cited in the application column 2, line 31 - line 54 example 2 claims --- -/--	1-15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 May 2000	11/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Epskamp, S

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Ir. ational Application No
PCT/US 99/29204

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 169 642 A (BRINKER DALE R ET AL) 8 December 1992 (1992-12-08) cited in the application column 1, line 49 -column 2, line 24 examples 1,2 claims	1-15
A	WO 98 47491 A (ODIDI AMINA ;ODIDI ISA (CA)) 29 October 1998 (1998-10-29) page 5, line 33 -page 6, line 2 page 12, line 22 -page 13, line 7 examples claims 1,4-7,10-16,29	1-13

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/29204

B x I Observation where certain claims were found unsearchable (C ntinuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 14 and 15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Im tional Application No
PCT/US 99/29204

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5019398 A	28-05-1991	FR 2643556 A	31-08-1990
		AU 623225 B	07-05-1992
		AU 4999890 A	30-08-1990
		CA 2010427 A	27-08-1990
		EP 0385846 A	05-09-1990
		NZ 232649 A	29-01-1991
US 5009897 A	23-04-1991	AT 82497 T	15-12-1992
		AU 3656189 A	04-01-1990
		CA 1335258 A	18-04-1995
		EP 0347748 A	27-12-1989
		ES 2052816 T	16-07-1994
		GR 3006537 T	30-06-1993
		IE 63242 B	05-04-1995
		JP 2045418 A	15-02-1990
		JP 2862567 B	03-03-1999
		US 5169642 A	08-12-1992
		US 5268182 A	07-12-1993
US 5169642 A	08-12-1992	US 5268182 A	07-12-1993
		AT 82497 T	15-12-1992
		AU 3656189 A	04-01-1990
		CA 1335258 A	18-04-1995
		EP 0347748 A	27-12-1989
		ES 2052816 T	16-07-1994
		GR 3006537 T	30-06-1993
		IE 63242 B	05-04-1995
		JP 2045418 A	15-02-1990
		JP 2862567 B	03-03-1999
		US 5009897 A	23-04-1991
		AT 112678 T	15-10-1994
		AU 623560 B	14-05-1992
		AU 6764390 A	14-02-1991
		CA 2031150 A	02-06-1991
		DE 69013296 D	17-11-1994
		DE 69013296 T	23-02-1995
		DK 430287 T	27-02-1995
		EP 0430287 A	05-06-1991
		ES 2065461 T	16-02-1995
		IE 66116 B	13-12-1995
		IL 96311 A	26-05-1995
		JP 3190817 A	20-08-1991
		PT 96046 A	13-09-1991
WO 9847491 A	29-10-1998	AU 6817098 A	13-11-1998
		CA 2216215 A	05-10-1998